

CGATGTCTGCACAAGGCTGTCACTCAGGTGGCAGTGGCTGACACGTGGCCGGGCAGCTCTGC
 TGCTGCGGCGCGAAGTCGAGAGGCGGCGGGGTCCGTGGCGCGCGCTCGCATTGCTCCGAGGC
 TCCGAGCGGCGATACGGGCGGGCGCCGACGGCAGGGTCTCCATGCCGCGCGTGGGGCGGGC
 CGCTGATGGAGCGCGCCACCCGGCCCGGGCCGCGCGCTGCTGCTGCTTCTGTTCTTGCTG
 CTGGGCTGCGCGGCGGGGATCTCTGCGGTGCGCGCCCGCCCGCAGTTTGCTTGCTCCCGCGTC
 GGAGACAGTGTGTTGGCTTAGGGGCAGCGGCCGCCCCGACTTCGGCCGCGCGGGTGCCGCGG
 TGGCAACGGCCGAAGTGACCGTGAGGACGCCGAGGCATTGCCGGCTGCCGCTGGCGAACCG
 GAGTCACGCGCGACGGAGCCCGATGACGACGTGGAACCTGCGGCCTCGCGGCAGGTCCTTGGT
 AATCATCAGCACTTTAGATGGACGAATCGCTGCACTGGATGCCGAGAATGATGGGAAAAAGC
 AGTGGGATTTGGACGTGGGGTCTGGTTCTTGGTTTCATCTAGCCTCAGCAAGCCAGAGGTG
 TTTGGGAACAAGATGATCATCCCTCCCTGGATGGAGACCTCTTCCAGTGGGACCGGGACCG
 AGAGAGCATGGAGGCCGTCCCTTACCGTGGAGTCCCTGCTCGAATCTTCTACAAGTTTG
 GAGATGATGTTGTTCTGGTTGGAGGGAAATCTCTGATTACATACGGACTCAGTGCTTACAGT
 GGAAAGCTGAGGTATATCTGTTCTGCCTTGGGATGTGCGCGATGGGATAGTGATGAAATGGA
 AGAAGAGGAAGACATCTTGCTTCTGCAGCGTACGCAGAAGACTGTGCGAGCTGTGCGGCCTC
 GAAGCGGCAGTGAGAAGTGGAATTTAGTGTGGCCACTTTGAACTTCGGTATATTCAGAC
 ATGGAACTAGAGCCGGATTTCATTGAAAGCACCTTTAAACCGGGTGAAACAAAGAAGACTC
 TAAAATTATTTAGATGTGGAAGAACAAGAAGCCACCATGCTGGACACAGTGATAAAAGTTT
 CCGTTGCTGATTGGAAGGTGATGGCGTTTAGTAGGAAGGAGGCCGCTGGAATGGGAGTAC
 CAGTTTTGTACTCCCATCGCGTCCGCTGGCTGGTGAGGGATGGCAAGGTGATCCCCATCAG
 CCTGTTTGATGATACAAGTTACACAGCCAGCGAAGAAGCCTTGGGAGACGAAGAAGACATTG
 TAGAGGCTGCTCGGGGAGCCACAGAGAACAGCGTGTACTTAGGGATGTACAGAGGCCAGCTG
 TACCTGCAGTCGTCCGTGAGGGTCTCAGAAAAGTTCCCTACAAGCCCAAAGGCCCTTGAGTC
 TGTAATGGCGAAAATGCAATTATTCTCTGCCGACGATCAAATGGAAGCCCTTAATCCATT
 CTCCTTCTAGGACTCCTGTCTTGGTTGGGTCTGATGAATTTGACAAATGTCTAAGTAATGAT
 AAGTATTTCCACGAAGAATACAGTAATGGTGCATTTCAATCCTCCAGTATCCATACGATAA
 CGGTTACTATCTGCCATACTACAAGAGAGAAAGGAATAAGCGGAGCACGCAGATCACAGTCA
 GGTTCCTGGACAGCCCCCACTACAGCAAGAACATCCGCAAGAAGGACCCTATCCTCCTGCTG
 CACTGGTGGAAAGGAGATATTCGGGACGATCCTGCTTTGCATCGTAGCCACGACCTTCATCGT
 GCGCAGGCTTTTCCATCCTCAGCCCCACAGGCAGCGGAAGGAGTCTGAAACTCAGTGCCAGA
 CTGAAAGTAAATACGACTCCGTGAGTGCCGATGTGAGTGACAACAGCTGGAATGACATGAAG
 TACTCAGGATACGTATCCCGATATCTAACAGATTTTGAGCCAATTCAGTGCATGGGTGCTGG
 TGGCTTTGGCGTTGTCTTTGAAGCTAAAAACAAAGTAGATGACTGCAATTACGCTATCAAGA
 GGATCCGGCTCCCCAACAGGGAGTTGGCACGGGAGAAGGTAATGCGGGAAGTTAAAGCCTTG
 GCTAAGCTGGAACACCCAGGCATTGTGAGGTATTTCAACGCCTGGCTGGAAACCCACCAGA
 GAAGTGGCAAGAAGAGATGGATGAGATCTGGCTCAAAGACGAAAGCACAGACTGGCCGCTCA
 GCTCCCCCTAGCCCGATGGATGCCCATCTGTTAAGATCCGAAGGATGGATCCYTTCTCTACA
 AAAGAGCAGATCGAAGTCATAGCTCCTTCTCCTGAAAGAAGTCGGTCTTTCTCGGTGGGCAT
 TTCCTGTGGCCAGACAAGCTCATCGGAGAGCCAGTTCTCTCCCCTGGAGTTCTCAGGGACAG
 ACTGCGGAGACAACAGTGACTCAGCGGACGCAGCCTACAACCTCCAGGACAGTTGCCTGACG
 GACTGCGAGGACGTGGAAGATGGCACCGTGGACGGCAATGACGAGGGACACTCCTTTGAACT
 TTGTCCGTCCGAAGCTTCTCCCTATACCCGGTCTAGGGAAGGAACGTCCTCCTCCATAGTGT
 TTGAGGACTCTGGCTGCGGCAACGCGTCCAGTAAGGAGGAGCCAGAGGGAACCGGCTGCAT
 GATGGCAACCATTATGTTAATAAGCTAACTGATCTCAAGTGCTCCAGCAGCAGGTCTTCTTC
 AAGAACACTGTGGGCCAGCTCCAGCCCAGCTCCCCCAAGGTGTATCTGTGAAGCCACCACCT
 TGTCTACCTCCCCTACCAGGCCAACCACTCTAAGCTTGGATTTACCAACATTGATGCAG

FIGURE 1A(1)

CTGTGCAGGAAGGAGAACCTCAAAGACTGGATGAACCGGCGCTGCAGCTTGGAGGACCGGGA
GCACGGCGTGTGCCTGCACATCTTCCTGCAGATCGCAGAGGCAGTGGAGTTCCTGCACAGCA
AGGGACTCATGCACAGGGACCTCAAGCCTTCCAACATATTCTTCACAATGGATGATGTGGTC
AAGGTTGGGGACTTTGGACTGGTGA CTGCTATGGACCAAGATGAAGAAGAGCAGACTGTTCT
GACTCCAATGCCAGCCTATGCTACGCACACGGGACAAGTAGGGACCAAGCTATACATGAGCC
CAGAGCAGATTCATGGAAACA ACTACTCCCATAAAGTGGACATCTTCTCTTTAGGCTTGATT
CTGTTTGAACCTCCTCTACCCATT CAGCACCCAGATGGAACGAGTCCGGATTTTAACTGATGT
CAGAAATCTCAAGTTTCTCTACTGTTCACTCAGAAATATCCCCAAGAGCATATGATGGTTC
AAGACATGCTCTCTCCATCCCCACGGAGCGGCCTGAAGCCACAGACATCATTGAAAATGCC
ATATTTGAGAACTTGGAGTTTCCCGGGAAAACGGTCTGAGACAGCGGTCCCGCTCCATGAG
TTCATCTGGAACAAAACATTCCAGACAGCCCAGCTGCTCGTACAGCCCACTGCCTGGCAACT
AGCCCTCAGCTGCCCTCGAAGGTGGCAGAGCAGGCACCCTGAGGAACATGGCTCTCCACAGC
GGTGGACTCAGATTTTATGCTTTGATCAGTTGGACTCGGGACCAATTTTTCTAAGTCAGACT
GGATCACGGGCCTAACCAGTTTGATCTTAACTGAACTTCAAGGAAAGGGCTGTGTAAAGGA
CACATGAACTTGTTGCTTGTGCGGTGTCCCAAGACTAGCTGGTCAGCTTAGAACCTTCACTTT
TCACCAGGCGGTAGAAGAGATCCTCAAATGGTCTGAACTGGAAATGTCTTTAAAGCACAAAA
GTGTAAAAGACCCTCTCACATGGGAACTACATGTTCTAGAAACGTGCTTTCTAGAGATACAA
GGGTGATTTTGGAAGTGGTTGTTATAAAGCTGACTTCATTTTTTTCCCTGGTGAGCCGTGAC
CCATCTGCACTAATTTGCAAGGCACATAGCACAAAGCTGGGTGCGCCATTTATGTCGGTAGTGT
CATAGTCTGCAGCAGTGAATAGCGTCATTCTTCAGGTGGTCTAGGGAGCGCGAAAAGCTTTT
TTGTACTTTTTTACCTCCAATAATGGGAAAATGAAGCTTTTAGGTATTGGTCAAAAAGATCTGA
TTTGAGAGTTTTTGGGTTTTTTTTTTTAAAGTGCAGTAGGAAATGGATTATCTATTACAAC TAAC
TTCTTCAATTATGGAATTTTTATCCTAGTAGAATTCTGTCTTAAATGTAATACTACAAGTGG
GTACATTCCCCAAACTGATTATAGATAAGTTTAATCATCTCAACTTGCTAACATGTTTTCA
TTTTTCTGTAAATACGTTTATTTTTTATTTATAAAAATTCTGAAATCAATCCATTTGGGTT
GGTGGTGTACAGAACGCACGTAAGTGTGATAACTATTATGACTTCTTTCAAGTCTAAATGAT
TTAATAAAAAAATTTTAAATTAAAAA AAAAAAAAAAAAAAAAAAAAAA (SEQ ID NO:1)

FIGURE 1A(2)

MERATRPGPRAALLLLFLLLGCAAGISAVAPARSLAPASETVFGLGAAAAP TSAARVPAVA
 TAEVTVEDAEALPAAAGEPESRATEPDDDVELRPRGRSLV IISTLDGRIAALDAENDGKKQW
 DLDVGSGSLVSSSLSKPEVFGNKM IIPSLDGDLFQWDRDRESMEAVPFTVESLLESSYKFGD
 DVVLVGGKSLITYGLSAYSGLRYIC SALGCRRWDSDEMEEEED ILLLQRTQKTVRAVGPRS
 GSEKWNFSVGHFELRYIPDMETRAGFIESTFKPGGNKEDSKIISDVEEQEATMLD TVIKVSV
 ADWKVMAFSRKGGRLWEYQFCTPIASAWLVRDGKVIPI SLFDDTSYTASEEALGDEEDIVE
 AARGATENSVYLGMYRGQLYLQSSVRVSEKFPTSPKALESVNGENAI IPLPTIKWKPLIHSP
 SRTPVLVGSDEFDKCLSNDKYSHEEYSNGALSILQYPYDNGYYLPYYKRERNKRSTQITVRF
 LDSPHYSKNIRKKDPILLHWWKEIFGTILLCIVATTFIVRRLFHPQPHRQRKESETQCQTE
 SKYDSVSADVSDNSWNDMKYSGYVSRYLTDFEPIQCMGRGGFGVVFEAKNKVDDCNYAIKRI
 RLPNRELAREKVMREVKALAKLEHPGIVRYFNAWLETPEKWQEEMDEIWLKDESTDWPLSS
 PSPMDAPSVKIRMDPFSTKEQIEVIAPSPERSRFSVSGISCGQTSSSESQFSPLEFSGTDC
 GDNSDSADAAYNLQDSCLTDCEDVEDGTVDGNDEGHSELC PSEASPYTRSREGTSSSIVFE
 DSGCGNASSKEEPRGNRLHDGNHYVNKLTDLKCSSSRSSSEATTLSTSPTRPTTSLDFTKN
 TVGQLQPSSPKVYLYIQMQLCRKENLKDWMNRCSLEDREHGVCLHIFLQIAEAVEFLHSGK
 LMHRDLKPSNIFFTMDDVVKVGDFGLVTAMDQDEEEQTVLTPMPAYATHTGQVGTKLYMSPE
 QIHGNNYSHKVDIFSLGLILFELLYPFSTQMERVRILT DVRNLKFPLLFTQKYPQEHMMVQD
 MLSPSPTERPEATDI IENAI FENLEFPGKTVLRQSRSMSSSGTKHSRQPSCSYSP LPGN
 (SEQ ID NO:2)

FIGURE 1B

underlined = deleted in targeting construct

[] = sequence flanking Neo insert in targeting construct

CGATGTCTGCACAAGGCTGTCACTCAGGTGGCAGTGGCTGACACGTGGCCGGGCAGCTCT
GCTGCTGCGGCGCAAGTCGAGAGGCGGCGGGTCCGTGGCGCGCGCTCGCATTGCTCCG
AGGCTCCGAGCGGCGATACGGGCGGGCGCGACGGCAGGGTCTCCATGCCCGCGCTGGG
GCGGGCCGCTGATGGAGCGGCCACCCGGCCCGGCGCGCGCTGCTGCTGCTTCTGT
TCCTGCTGCTGGGCTGCGCGGCGGGGATCTCTGCGGTGCGCGCCCGCCGAGTTTGCTTG
CTCCCGCGTTCGAGACAGTGTGTTGGCTTAGGGGACGCGCGCCCGGACTTCGGCCGCGC
GGGTGCTGCGGTGGCAACGGCCGAAGTGACCGTGAGGACGCGGAGGCATTGCCGGCTG
CCGCTGGCGAACCGGAGTCACGCGGACGAGCCCGATGACGACGTGGAAGTGC GGCCCTC
GCGGCAGGTCTTTGGTAATCATCAGCACTTTAGATGGACGAATCGCTGCACTGGATGCCG
AGAATGATGGGAAAAAGCAGTGGGATTGACGTGGGGTCTGGTTCCTTGGTTTTCATCTA
GCCTCAGCAAGCCAGAGGTGTTTGGGAACAAGATGATCATCCCCCTCCCTGGATGGAGACC
TCTTCCAGTGGGACCGGGACCGAGAGAGCATGGAGGCCGTCCCCTTACGGTGGAGTCCC
TGCTCGAATCTTCTACAAAGTTTGGAGATGATGTGTTCTGGTGGAGGGAAATCTCTGA
TTACATACGGACTCAGTGCTTACAGTGGAAAGCTGAGGTATATCTGTTCTGCCTTGGGAT
GTCGCGGATGGGATAGTGATGAAATGGAAGAAGAGGAAGACATCTTGCTTCTGCAGCGTA
CGCAGAAGACTGTGCGAGCTGTGCGGCCCTCGAAGCGGCAGTGAGAAGTGAATTTAGTG
TTGGCCACTTTGAACTTCGGTATATTCCAGACATGAAAGTGGAGCCGATTGATTGAAA
GCACCTTTAAACCGGGTGGAAACAAAGAAGACTCTAAATATTATTCAGATGTGGAAGAAC
AAGAAGCCACCATGCTGGACACAGTGATAAAAGTTTCCGTTGCTGATTGGAAGGTCATGG
CGTTTAGTAGGAAGGGAGGCCGCTGGAATGGGAGTACAGTTTGTACTCCCATCGCGT
CCGCTTGGCTGCTGAGGGATGGCAAGGTCTATCCCCATCAGCCTGTTTGTATGATACAAGTT
ACACAGCCAGCGAAGAAGCCTTGGGAGACGAAGAAGACATTGTAGAGGCTGCTCGGGGAG
CCACAGAGAACAGCGTGTACTTAGGGATGTACAGAGGCCAGCTGTACCTGCAGTCGTCCG
TCAGGGTCTCAGAAAAGTTCCCTACAAGCCCAAGGCCTTGGAGTCTGTAAATGGCGAAA
ATGCAATTATTCTCTGCCGACGATCAAATGGAAGCCCTTAATCCATTCTCCTTCTAGGA
CTCCTGTCTTGGTTGGGTCTGATGAATTTGACAAATGTCTAAGTAATGATAAGTATTCCC
ACGAAGAATACAGTAATGGTGCACTTTCAATCCTCCAGTATCCATACGATAACGGTTACT
ATCTGCCATACTACAAGAGAGAAAGGAATAAGCGGAGCACGCAGATCACAGTCAGGTTCC
TGGACAGCCCCACTACAGCAAGAACATCCGCAAGAAGGACCCTATCCTCCTGCTGCACT
GGTGAAGGAGATATTCCGGACGATCCTGCTTTCATCGTAGCCACGACCTTCATCGTGC
GCAGGCTTTTCCATCCTCAGCCCCACAGGCAGCGAAGGAGTCTGAAACTCAGTGCCAGA
CTGAAAGTAAATACGACTCCGTGAGTGCCGATGTGAGTGACAACAGCTGGAATGACATGA
AGTACTCAGGATACGTATCCCGATATCTAACAGATTTTGAGCCAATTCAGTGCATGGGTC
GTGGTGGCTTTGGCGTTGTCTTTGAAGCTAAAAACAAAGTAGATGACTGCAATTACGCTA
TCAAGAGGATCCGGCTCCCCAACAGGGAGTTGGCACGGGAGAAGGTAATGCGGGAAGTTA
AAGCCTTGGCTAAGCTGGAACACCCAGGCATTGTGAGGTATTTCAACGCCTGGCTGGAAA
CCCCACCAGAGAAGTGGCAAGAAGAGATGGATGAGATCTGGCTCAAAGACGAAAGCACAG
ACTGGCCGCTCAGCTCCCCTAGCCGATGGATGCCCCATCTGTTAAGATCCGAAGGATGG
ATCCYTTCTTACAAAAGAGCAGATCGAAGTCATAGCTCCTTCTCCTGAAAGAAGTCGGT
CTTTCTCGGTGGGCATTTCTGTGGCCAGACAAGCTCATCGGAGAGCCAGTTCTCTCCCC
TGGAGTTCTCAGGGACAGACTGCGGAGACAACAGTGACTCAGCGGACGCAGCCTACAACC
TCCAGGACAGTTGCCTGACGGACTGCGAGGACGTGGAAGATGGCACCGTGGACGGCAATG
ACGAGGGACACTCCTTTGAACTTTGTCCGTCCGAAGCTTCTCCC [TATACCCGGTCTAGG

FIGURE 2A(1)

GAAGGAACGTCCTCCTCCATAGTGTGTTGAGGACTCTGGCTGCGGCAACGCGTCCAGTAAG
 GAGGAGCCCAGAGGGAACCGGCTGCATGATGGCAACCATTATGTTAATAAGCTAACTGAT
 CTC AAGTGCTCCAGCAGCAGGTCTTCTTCAGAAGCCACCACCTTGTCTACCTCCCCTACC
 AGGCCAACCACCTCTAAGCTTGGATTTACCAAGAACACTGTGGGCCAGCTCCAGCCCAGC
 TCCCCAAGGTGTATCTGTACATTAGATGCAGCTGTGCAGGAAGGAGAACCCTC] AAAGA
CTGGATGAACCGGCGCTGCAGCTTGGAGGACCGGGAGCACGGCGTGTGCCTGCACATCTT
CCTGCAGATCGCAGAGGCAGTGGAGTTCTCTGCAC [AGCAAGGGACTCATGCACAGGGACC
 TCAAG] CCTTCCAACATATTCTTCACAATGGATGATGTGGTCAAGGTTGGGGACTTTGGA
 CTGGTGACTGCTATGGACCAAGATGAAGAAGAGCAGACTGTTCTGACTCCAATGCCAGCC
 TATGCTACGCACACGGGACAAGTAGGGACCAAGCTATACATGAGCCCAGAGCAGATTTCAT
 GGAAACAACTACTCCCATAAAGTGGACATCTTCTCTTTAGGCTTGATTCTGTTTGAACCTC
 CTCTACCCATTAGCAGCCAGATGGAACGAGTCCGGATTTTAACTGATGTCAGAAATCTC
 AAGTTTCCTCTACTGTTCACCTCAGAAATATCCCCAAGAGCATATGATGGTTCAAGACATG
 CTCTCTCCATCCCCACGGAGCGGCTGAAGCCACAGACATCATTGAAAATGCCATATTT
 GAGAACTTGGAGTTTCCCGGAAAAACGGTCTGAGACAGCGGTCCCGCTCCATGAGTTCA
 TCTGGAACAAAACATTCCAGACAGCCCAGCTGCTCGTACAGCCCAGTGCCTGGCAACTAG
 CCCTCAGCTGCCCTCGAAGGTGGCAGAGCAGGCACCCTGAGGAACATGGCTCTCCACAGC
 GGTGGACTCAGATTTTATGCTTTGATCAGTTGGACTCGGGACCAATTTTCTAAGTCAGA
 CTGGATCACGGGCCTAACCCAGTTTGATCTTAACTGAACTTCAAGGAAAGGGCTGTGTAA
 AGGACACATGAACTTGTTGCTTGTGCGGTGTCCCAAGACTAGCTGGTCAGCTTAGAACCTT
 CACTTTTCACCAGGCGGTAGAAGAGATCCTCAAATGGTCTGAACTGGAAATGTCTTTAAA
 GCACAAAAGTGTAAGAGACCCCTCTCACATGGGAACTACATGTTCTAGAAACGTGCTTTCT
 AGAGATACAAGGGTGATTTTGAAGTGGTTGTTATAAAGCTGACTTCATTTTTTCCCTG
 GTGAGCCGTGACCCATCTGCACTAATTTGCAAGGCACATAGCACAAAGCTGGGTGCGCATT
 TATGTCGGTAGTGTCATAGTCTGCAGCAGTGAATAGCGTCATTCTTCAGGTGGTCTAGGG
 AGCGCGAAAAGCTTTTTTGTACTTTTTACCTCCAATAATGGGAAAATGAAGCTTTTAGGT
 ATTGGTCAAAAGATCTGATTTGAGAGTTTTGGGTTTTTTTTTTAAGTCAGTAGGAAATG
 GATTATCTATTACAATACTTCTTCAATTATGGAATTTTTATCCTAGTAGAATTCTGTC
 TTAATGTAATACTACAAGTGGGTACATTCCCCAACTGATTATAGATAAGTTTAATCA
 TCTCAACTTGCTAACATGTTTTCATTTTTCTGTAAATACGTTTATTTTTATTTATAAA
 AATTCGAAATCAATCCATTTGGGTGGTGGTGTACAGAACGCACGTAAGTGTGATAACT
 ATTATGACTTCTTTCAAGTCTAAATGATTTAATAAAAAAATTTAAATTAAAAA
 AAAAAAAAAA

FIGURE 2A(2)

Gene Sequence Structure *

2874 bp

Sequence Deleted

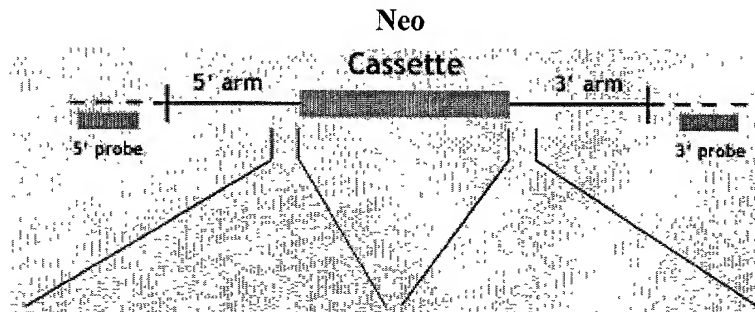
2972 bp

Size of full-length
cDNA: 4510 bp



Targeting Vector* (genomic sequence)

Arm Length:
5': 2.4 kb
3': 1.3 kb



— Targeting Vector
- - - Endogenous Locus
* Not drawn to scale

5' > ACCATTATGTTAATAAGCTAA
CTGATCTCAAGTGCTCCAGCAGCA
GGTCTTCTTCAGAAGCCACCACCT
TGTCTACCTCCCCTACCAGGCCAA
CCACTCTAAGCTTGGATTTCACCA
AGAACTGTGGGCCAGCTCCAGC
CCAGCTCCCCCAAGGTGTATCTGT
ACATTGAGATGCAGCTGTGCAGGA
AGGAGAACCTC<3' (SEQ ID
NO: 3)

5' > AGCAAGGGACTCATGCACGGG
ACCTCAAGGTCTGTAGCCAGAGGC
GGCCACGCCGGGCTTTGGGTGTGC
CCTGGGGTTCAGAGCAGAGGTCGG
GGAAGGAAGCAGGGAAGGAAGAAG
TTCATATGTAAAGGCTCAGGCA
GACTGTGCATCTTCCTTTACGGCC
TGTTTATTTTGTCTTACTGTAAA
CACTGTTTCCA<3' (SEQ ID
NO: 4)

FIGURE 2B

Phenotypic Data Summary - Metrazol

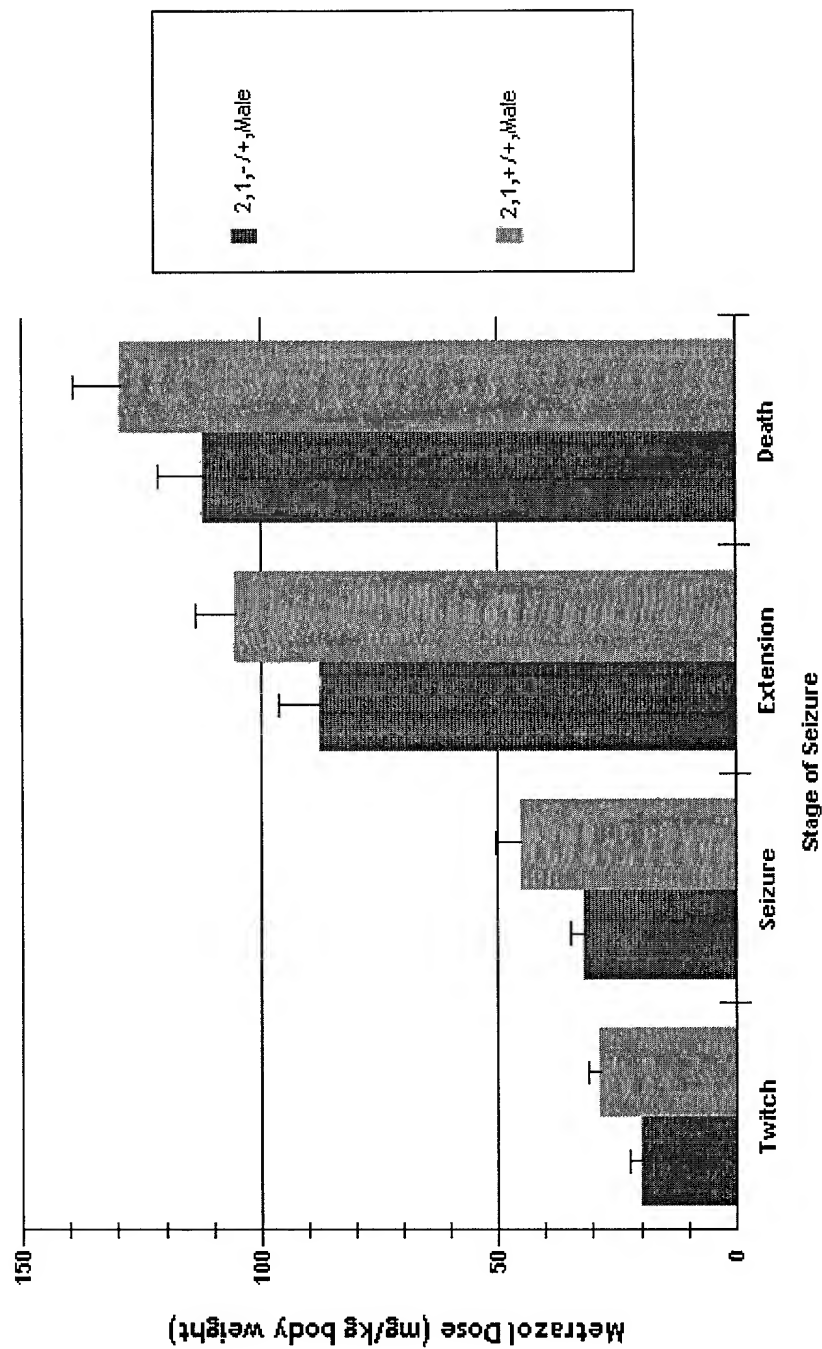


FIGURE 3